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DOES IT MAKE SENSE TO DEVELOP NEW CENTRALLY ACTING CARDIOVASCULAR DRUGS?

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SUMMARY

1. The autonomic nervous system plays a pivotal role in modulating all the components of the cardiovascular regulation. Therefore, one can assume that drugs targeting this system may be useful in the management of several cardiovascular diseases.

2. Drugs acting on central nervous system centres seem to be modulators rather than blockers; as such, they are expected to preserve the contraregulatory processes and to generate only a few side effects.

3. Because the sympathetic nervous system is largely involved in the regulation of vasomotor tone, centrally acting antihypertensive drugs were developed first.

4. Recently, new leader compounds selective for non-adrenergic imidazoline recepetors have been synthetized. Although such drugs have no capacity to activate α_2-adrenoceptors, they have been proven to be hypotensive. These drugs are expected to be even better tolerated than the currently available centrally active drugs. They may also have additional beneficial effects.

5. Here, the experimental evidence suggesting that such drugs may be useful in the management of some cardiac arrhythmias and/or left ventricular dysfunction will be reviewed.

Key words: autonomic nervous system, cardiac arrhythmias, congestive heart failure, hypertension, imidazolines.

INTRODUCTION

Interest in the autonomic nervous system (ANS) as a target for cardiovascular drugs has recently been strengthened for several reasons. Not only has a second-generation class of centrally acting antihypertensive drugs efficient as first-line well-tolerated drugs been introduced (e.g. rilmenidine and moxonidine),[1] but also several indices related to ANS activity have been shown[2,3] to predict the prognosis of some cardiovascular diseases. Thus, plasma noradrenaline levels are correlated with the severity of congestive heart failure (CHF) and variabilities in blood pressure and heart rate, which depend to a great extent on ANS activity, are often proposed as cardiovascular morbidity and/or mortality predictors.[4,5] Recently, beta-blocking drugs have been introduced for the management of heart failure, despite the fact that they have been contraindicated in this field for at least three decades. Increasing interest is now directed towards the metabolic syndrome that associates hypertension, sympathetic hyperactivity and hyperinsulinaemia, in particular to the sympathetic component of this syndrome. Finally, very recently new leader compounds that act centrally but on original pharmacological targets have become available.[6,7]

The present review will summarize some of the arguments supporting the contention that drugs acting within sympathetic centres may be of interest for the management not only of hypertension but also cardiac arrhythmias and CHF. In fact, these pathologies are often interwoven through a sympathetic hyperactivity. In these cases, well-tolerated centrally acting sympathoinhibitors would be of major interest. So far, only a few studies have been undertaken to assess the potential of such drugs in this metabolic syndrome and myocardial ischaemia; that is why these pathologies will be omitted in the present review.

TOWARDS A THIRD GENERATION OF CENTRALLY ANTIHYPERTENSIVE DRUGS?

A long time ago, we demonstrated that, compared with α-methyl noradrenaline, the active metabolite of α-methyl dihydroxyphenylalanine (DOPA), imidazoline compounds, such as clonidine, have a different site of action within the brainstem.[8] These drugs also have a different mechanism of action.[9] Recently, we reported new evidence for these differences. Pretreatment with nitro-L-arginine given centrally completely abolished the hypotensive effect of α-methyl noradrenaline. In contrast, inhibition of nitric oxide synthase had no effect on the clonidine-induced decrease in blood pressure.[10] Nitric oxide (NO) is required for the release process of several neurotransmitters within the central nervous system. A GABAergic pathway coming from the nucleus tractus solitarius (NTS) projects to the nucleus reticularis of the rostroventrolateral part of the medulla. Therefore, our data are consistent with the view that α-methyl noradrenaline, which is known to stimulate α_2-adrenoceptors of the NTS, stimulates this pathway and activates NO-dependent GABA release within the nucleus reticularis area. Finally, GABA will inhibit the so-called cardiovascular sympathetic neurons in this particular nucleus. Because clonidine and related compounds inhibit these neurons by acting directly within the nucleus reticularis, they do not need NO. The latter action is mediated by non-adrenoceptors called imidazoline receptors, whereas the side effects of the clonidine-like drugs were clearly attributed to

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their remaining capacity to stimulate α_2-adrenoceptors.[1] Therefore, considerable efforts were made to synthetize compounds selective for these non-adrenoceptors. Very recently, a series of such drugs became available. We described that two representatives of these kinds of drugs, namely LNP 509 and S23515, with no detectable affinity for and no activity at α_2-adrenoceptors, were able to decrease blood pressure when delivered centrally.[6,7] At the present time, compounds LNP 509 and S23515 are the leaders in the development of a third generation of centrally acting antihypertensive drugs. Preliminary animal experiments (P Bousquet *et al.*, unpubl. obs., 2001) have shown that, as expected, these drugs have no sedative effects at hypotensive doses.

CENTRAL ANTI-ARRHYTHMIC EFFECTS

Rilmenidine is an oxazoline, that is, an analogue of imidazoline compounds such as clonidine. Rilmenidine has proved useful in treating mild to moderate hypertension, with an acceptability similar to that of more recent classes of antihypertensive drugs (e.g. angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists) or to that of a placebo.[1] One of the risks associated with hypertensive diseases is that of ventricular arrhythmias, which are observed in approximately 30% of patients. These arrhythmias usually occur in patients with left ventricular hypertrophy. They may result in sudden death.[11–14]

In rabbits, arrhythmias of central origin associated with sympathetic hyperactivity were induced by central (intracisternal) injection of the $GABA_A$ receptor antagonist bicuculline. In this model, rilmenidine reduces the occurrence of ventricular arrhythmias in a dose-dependent manner.[15] Bicuculline, delivered intracisternally, evoked a marked hypertensive response accompanied by ventricular ectopic beats, episodes of ventricular tachycardia evolving into a sustained tachycardia and, finally, fibrillation, which is fatal in the absence of treatment. Pretreatment of these animals with cumulative doses (10 μg/kg to 1 mg/kg) of intravenous rilmenidine significantly prevented the occurrence of all bicuculline-induced arrhythmic events in a dose-dependent manner.[15] Rilmenidine given intracisternally (10–30 μg/kg) had very similar cardioprotective effects. It is interesting to note that, in this experimental model, rilmenidine had anti-arrhythmic effects even at doses lower than those needed to decrease blood pressure.[15] In addition, treatment with idazoxan, a selective imidazoline antagonist, confirmed that the anti-arrhythmic effect of rilmenidine involves imidazoline-specific receptors.[15] Our results were consistent with those of Mammoto *et al.*, who have reported that rilmenidine prevents the occurrence of ventricular arrhythmias induced by a mixture of halothane and adrenaline.[16]

Thus, centrally acting drugs are potentially useful as anti-arrhythmics even at doses devoid of any hypotensive action.

Very recently, drugs selective for imidazoline receptors over α_2-adrenoceptors were synthesized in our laboratory.[7] For instance, preliminary data show that LNP 509 has no action at α_2-adrenoceptors but that it does have a remarkable preventing effect against bicuculline-induced ventricular arrhythmias in rabbits (J Feldman *et al.*, unpubl. obs., 2001).

Thus, a novel class of centrally acting anti-arrhythmic drugs takes shape. Because, according to the results of the Cardiac Arrhythmias Suppression Trial (CAST) study,[17,18] most available anti-arrhythmic drugs are of restricted use given their adverse effects (in particular their paradoxical pro-arrhythmic actions), a new class of anti-arrhythmic drugs devoid of such side effects would be extremely valuable.

LEFT VENTRICULAR DYSFUNCTION: CONGESTIVE HEART FAILURE

An interesting debate has been going on regarding the treatment of CHF. We tackled this subject keeping in mind the observation that sympathetic activation is associated with severe left ventricular failure. Although this sympathetic hyperactivity is a compensatory process, it also accelerates the progression of the disease and increases the morbidity and mortality due to CHF. Plasma levels of noradrenaline are a predictive index of the evolution of the disease.[19] The overall result of the alterations associated with CHF[20] is, in fact, an elevation of systemic vascular resistance, this being still further aggravated by activation of the renin–angiotensin–aldosterone system as a result of sympathetic stimulation. As far as left ventricular ejection fraction (LVEF) is concerned, this functional cascade is critical.

All drugs available that are used to treat CHF have their own restrictions.[20–22]

The potential interest of centrally acting drugs in the treatment of CHF is quite obvious. Drugs that specifically inhibit sympathetic activity would reduce the release of noradrenaline and adrenaline from the adrenal glands and, as a result, would diminish systemic vascular resistance and prevent activation of the renin–angiotensin–aldosterone system. All these effects would improve diastolic function and restore LVEF.[23] In addition, centrally acting drugs that not only inhibit sympathetic activity but also facilitate vagal activity would contribute to normalizing heart rate variability. There are already clinical data obtained for clonidine and α-methyl DOPA confirming the potential interest of centrally acting drugs in the treatment of heart failure.[24–27]

In Goldblatt hypertensive rats (one kidney, one clip), clonidine, for example, not only improves the life span and haemodynamic features of the rats, but it also has a promising anti-apoptotic effect in the myocardium (L Thomas *et al.*, unpubl. obs., 2001). The second generation of centrally acting sympathoinhibitory drugs has few side effects. For example, these drugs have neither negative inotropic effects, at least at reasonable doses, nor do they affect lipid and glucose metabolism.[1] Whether such drugs may be useful in the treatment of CHF at non-hypotensive doses remains to be demonstrated. Moreover, selective drugs, such as LNP 509, will be tested, of course, in CHF models.

CONCLUSIONS

The additional cardioprotective effects (anti-arrhythmic and prevention of left ventricular dysfunction) of second-generation centrally acting antihypertensive drugs should not be passed over in the further development of this new class of drugs.

The additional beneficial effects controlling risk factors associated with hypertension should boost the development of new centrally acting antihypertensive drugs. Henceforth, imidazoline-like drugs that do not act at α_2-adrenoceptors at all are leader compounds in the development of well-tolerated new antihypertensive agents. Interest in this class of drugs will be improved further when clinical

trials have confirmed that these drugs may have cardioprotective actions in patients.

Finally, because the anti-arrhythmic effects and improvement in LVEF induced by these sympathoinhibitory drugs are observed even when blood pressure is not altered, we can assume that centrally cardioprotective but non-hypotensive substances will be developed as drugs in the near future.

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Respective contributions of alpha-adrenergic and non-adrenergic mechanisms in the hypotensive effect of imidazoline-like drugs.

Bruban V, Feldman J, Greney H, Dontenwill M, Schann S, Jarry C, Payard M, Bo Scalbert E, Pfeiffer B, Renard P, Vanhoutte P, Bousquet P.

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The hypotensive effect of imidazoline-like drugs, such as clonidine, was first attributed exclusive stimulation of central alpha2-adrenoceptors (alpha2ARs). However, a body of evidence suggests that non-adrenergic mechanisms may also account for this hypotensi work aims (i) to check whether imidazoline-like drugs with no alpha2-adrenergic agoni activity may alter blood pressure (BP) and (ii) to seek a possible interaction between su and an alpha2ARs agonist alpha-methylnoradrenaline (alpha-MNA). We selected S235 S23757, two imidazoline-like drugs with negligible affinities and activities at alpha2AR with high affinities for non-adrenergic imidazoline binding sites (IBS). S23515 decreas dose-dependently (-27+/-5% maximal effect) when administered intracisternally (i.c.) t anaesthetized rabbits. The hypotension induced by S23515 (100 microg kg(-1) i.c.) was prevented by S23757 (1 mg kg(-1) i.c.) and efaroxan (10 microg kg(-1) i.c.), while thes compounds, devoid of haemodynamic action by themselves, did not alter the hypotensi of alpha-MNA (3 and 30 microg kg(-1) i.c.). Moreover, the alpha2ARs antagonist rauw (3 microg kg(-1) i.c.) did not prevent the effect of S23515. Finally, whilst 3 microg kg(- S23515 or 0.5 microg kg(-1) of alpha-MNA had weak hypotensive effects, the sequenti administration of these two drugs induced a marked hypotension (-23+/-2%). These res indicate that an imidazoline-like drug with no alpha2-adrenergic properties lowers BP a interacts synergistically with an alpha(ARs agonist.

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Imidazoline binding sites (IBS) profile modulation: key role of the br determining I1-IBS or I2-IBS selectivity within a series of 2-phenoxymethylimidazoline analogues.

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The alpha- and beta-methyl derivatives of 2-phenylethylimidazoline (compounds 7 and the corresponding enantiomers were prepared and tested with the purpose of studying th played by the ethylene bridge in modulating I(1)- and I(2)-IBS selectivity. The alpha-methylation appeared to be extremely critical regarding the affinity and selectivity for t subtypes (I1/I2 = 186 for imidazoline 7) and the stereospecificity of interaction (eudism (S)-(-)-7/(R)-(+)-7 = 5888). Instead, even if in a more limited fashion, the -methylation toward I2-IBS selectivity (I2/I1 = 50 for imidazoline 8). The unsubstituted compound 4 1479) proved to be considerably more potent and selective with respect to I2-IBS subty

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